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(54) Title: **USE OF CYCLOOXYGENASE 2 INHIBITOR AND AN INTEGRIN ANTAGONIST AS A COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA**

(57) Abstract: The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2 inhibitor, an integrin antagonist and an antineoplastic agent.

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INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 99/30692

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K41/00 A61P35/00 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 16227 A (GORDON GARY B ;SEARLE & CO (US); SEIBERT KAREN (US); MASFERRER JAI) 23 April 1998 (1998-04-23) cited in the application page 3, line 1-8 page 24, line 19-29 page 29, line 5,6 abstract claims 1-20 ---	1-140, 142
Y	WO 98 31359 A (DUGGAN MARK E ;MERCK & CO INC (US)) 23 July 1998 (1998-07-23) cited in the application claims 21-25 page 20, line 14-21 --- -/--	1-140, 142

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Intern. Patent Application No

PCT/US 99/30692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 98 14192 A (COUSINS RUSSELL DONOVAN ;SMITHKLINE BEECHAM CORP (US); KWON CHET () 9 April 1998 (1998-04-09) cited in the application page 6, line 12-24, 33-35 -----</p>	<p>1-140, 142</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/30692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 140, 142

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims relate to an extremely large number of possible methods and combinations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the methods and combinations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the methods and combinations referring to the general concept of the application, i.e. the combined use of integrin antagonists, COX-2 inhibitors as defined in the dependent claims and antineoplastic agents as defined in claim 1, further combined with radiation when applicable for the treatment or prevention of neoplasia.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-140,142

Use of an integrin antagonist together with a COX-2 inhibitor and an antineoplastic agents as defined in claim 1, optionally together with radiation, in the treatment of neoplasia

2. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.1 to 141.10 and 144.1 to 144.10 together with a COX-2 inhibitor in the treatment of neoplasia

3. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.11 and 144.11 together with a COX-2 inhibitor in the treatment of neoplasia

4. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.12 and 144.12 together with a COX-2 inhibitor in the treatment of neoplasia

5. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.13 and 144.13 together with a COX-2 inhibitor in the treatment of neoplasia

6. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.14, 141.15, 144.14 and 144.15 together with a COX-2 inhibitor in the treatment of neoplasia

7. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.16 and 144.16 together with a COX-2 inhibitor in the treatment of neoplasia

8. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.17, 141.18, 144.17 and 144.18 together with a COX-2 inhibitor in the treatment of neoplasia

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.19 and 144.19 together with a COX-2 inhibitor in the treatment of neoplasia

10. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.20-22 and 144.20-22 together with a COX-2 inhibitor in the treatment of neoplasia

11. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.23 and 144.23 together with a COX-2 inhibitor in the treatment of neoplasia antibody (Ixsys) in the treatment of neoplasia

12. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.24 and 144.25 together with a COX-2 inhibitor in the treatment of neoplasia

13. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.26 and 144.26 together with a COX-2 inhibitor in the treatment of neoplasia

14. Claims: 1141,144 (partly)

Use of an integrin antagonist as defined in claims 141.27 and 144.27 together with a COX-2 inhibitor in the treatment of neoplasia

15. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.28 and 144.28 together with a COX-2 inhibitor in the treatment of neoplasia

16. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.29 and 144.29 together with a COX-2 inhibitor in the treatment

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

of neoplasia

17. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.31 and 144.31 together with a COX-2 inhibitor in the treatment of neoplasia

18. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.32 and 144.32 together with a COX-2 inhibitor in the treatment of neoplasia

19. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.33 and 144.33 together with a COX-2 inhibitor in the treatment of neoplasia

20. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.34 and 144.34 together with a COX-2 inhibitor in the treatment of neoplasia

21. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.35, 141.36, 144.35 and 144.36 together with a COX-2 inhibitor in the treatment of neoplasia

22. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.37-43 and 144.37-43 together with a COX-2 inhibitor in the treatment of neoplasia

23. Claims: 141,144 (partly)

Use of an integrin antagonist as defined in claims 141.30 and 144.30 together with a COX-2 inhibitor in the treatment of neoplasia

24. Claim : 143

Use of an integrin antagonist as defined in claim 141

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

together with a COX-2 inhibitor and radiation in the treatment of neoplasia

25. Claims: 141, 144 (partly)

Use of an integrin antagonist as defined in claims 141.24 and 144.24 together with a COX-2 inhibitor in the treatment of neoplasia

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. .nal Application No

PCT/US 99/30692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9816227 A	23-04-1998	AU 4904897 A BR 9712314 A CN 1244122 A CZ 9901171 A EP 0932402 A NO 991793 A	11-05-1998 31-08-1999 09-02-2000 14-07-1999 04-08-1999 15-04-1999
W0 9831359 A	23-07-1998	AU 6023198 A EP 1007026 A	07-08-1998 14-06-2000
W0 9814192 A	09-04-1998	AU 4746297 A BG 103299 A BR 9712248 A CN 1238689 A EP 0957917 A HU 9903769 A NO 991590 A PL 332674 A SK 42599 A	24-04-1998 31-01-2000 24-08-1999 15-12-1999 24-11-1999 28-03-2000 31-05-1999 27-09-1999 10-12-1999